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REVIEW

Gastrointestinal neuroendocrine peptides/amines in inflammatory bowel disease

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Abstract

Inflammatory bowel disease (IBD) is a chronic recurrent condition whose etiology is unknown, and it includes ulcerative colitis, Crohn's disease, and microscopic colitis. These three diseases differ in clinical manifestations, courses, and prognoses. IBD reduces the patients' quality of life and is an economic burden to both the patients and society. Interactions between the gastrointestinal (GI) neuroendocrine peptides/amines (NEPA) and the immune system are believed to play an important role in the pathophysiology of IBD. Moreover, the interaction between GI NEPA and intestinal microbiota appears to play also a pivotal role in the pathophysiology of IBD. This review summarizes the available data on GI NEPA in IBD, and speculates on their possible role in the pathophysiology and the potential use of this information when developing treatments. GI NEPA serotonin, the neuropeptide Y family, and substance P are proinflammatory, while the chromogranin/secretogranin family, vasoactive intestinal peptide, somatostatin, and ghrelin are anti-inflammatory. Several innate and adaptive immune cells express these NEPA and/or have receptors to them. The GI NEPA are affected in patients with IBD and in animal models of human IBD. The GI NEPA are potentially useful for the diagnosis and follow-up of the activity of IBD, and are candidate targets for treatments of this disease.

Key words: Enteric nervous system; Enteroendocrine cells; Immune cells; Inflammatory bowel disease; Musashi-1; Neurogenin 3; Stem cells

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Core tip: Approximately 80% of the body immune cells (IC) are localized in the gastrointestinal (GI) tract close to the GI neuroendocrine regulatory system (NES). Many IC express GI neuroendocrine peptides/amines (NEPA) and possess receptors to several NEPA. Several GI NEPA are abnormal during active inflammatory bowel disease (IBD) in both patients and animal models of IBD. The changes in the GI NEPA are correlated with those of the IC during the inflammatory process. Studying the interactions between the GI NES and the immune system in IBD may improve our understanding of the pathophysiology of IBD and provide us with new tools for treatment.

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INTRODUCTION

Inflammatory bowel disease (IBD) is a lifelong recurrent disorder that comprises three diseases: ulcerative colitis (UC), Crohn's disease (CD), and microscopic colitis (MC). These three diseases have different clinical manifestations, courses, and prognoses[1-3]. Whereas the onset of UC and CD occurs mostly at a young age, MC onset occurs in old age[4,5]. In UC and CD, the activity of the disease varies considerably between patients, from frequent relapses, persistent active disease, to several years of complete remission[4], whereas all MC patients exhibit chronic active disease[6-8]. The inflammation in CD is transmural, in UC it is superficial, and in MC it is in the form of the mucosal and submucosal infiltration of immune cells (IC). CD can arise at any part of the gastrointestinal (GI) tract, while UC and MC affect the recto-colonic mucosa[8,9]. In contrast to UC and CD, spontaneous symptomatic remission occurs in 59%-93% of MC patients[10,11].

IBD diminishes the quality of life considerably and represents an economic problem to both the patients themselves and society[4,9]. The prevalence of IBD amounts to 1.4 million patients in North America and 2.2 million patients in Europe, with 3-20 new cases occurring per 100000 persons annually[12-16]. The prevalence of IBD does not differ among Hispanics, blacks, and Caucasians[17,18]. The incidence of IBD is lower in Asia than in North America and Europe[19-21], but it has been increasing worldwide in recent years[19,21].

The etiology of IBD is not completely understood[9], and the available treatments are not ideal[1-4,22-31]. Typically 70%-80% of the body IC are present in the GI tract in close proximity to the GI neuroendocrine regulatory system (NES)[32,33]. Interactions between the GI neuroendocrine peptides/amines (NEPA) and the immune system have recently been discussed, and it is believed that these interactions play an important part in the pathophysiology of IBD[33-45]. Understanding the role of the GI NEPA in IBD would increase our understanding of the mechanisms underlying the pathophysiology of IBD, and may yield tools for treating these conditions using agonists or antagonists to the GI NEPA[43].

The aim of the present review was to summarize the available data on GI NEA in IBD and to speculate on their possible role in the underlying pathophysiology, and the potential utilization of these peptides/amines in treatments.

GI NES

The NES comprises two parts: the GI endocrine cells in the mucosa and the enteric nervous system (ENS) (Figure 1). The GI endocrine cells occur in all segments of the GI tract except for the esophagus[46,47]. These cells lie between the mucosal epithelial cells facing the GI lumen, and they comprise about 1% of all epithelial cells and produce a large number of hormonal peptides/amines[48-56]. The GI endocrine cells are divided into at least 15 different types depending on the hormone they produce[48,49]. Two hormones can be colocalized in the same type of endocrine cell, such as glucagon-like peptide-1 and glucose-stimulated insulinotropic peptide in the small intestine, and peptide YY (PYY) and oxyntomodulin (enteroglucagon) in the distal small and large intestines[57-60]. It has been shown recently that mature GI endocrine cells can express up to seven different hormones[51,52,61-64].

The GI endocrine cells have specialized sensory microvilli that project into the lumen, and they respond to luminal stimuli (mostly nutrients and/or bacteria byproducts) by releasing their hormones into the lamina propria[32,42,65-85]. The cells also possess a basal cytoplasmic process about 70 μm long that is believed to be involved in their paracrine mode of action[86-90]. It has been shown recently that this process exhibits neuronal axon-like characteristics, and it has been named a neuropod[88,91-93]. The GI endocrine cells also exhibit synaptic vesicles and synthetize presynaptic proteins: synapsin 1, piccolo, bassoon, MUNC13B, RIMS2, latrophilin, and transsynaptic neurexin[88,91-93]. These cells also synthetize transsynaptic neuroligins 2 and 3, homer 3, and postsynaptic density 95[93]. Thus, the GI endocrine cells possess the elements necessary for both afferent and efferent synaptic transmission[93].

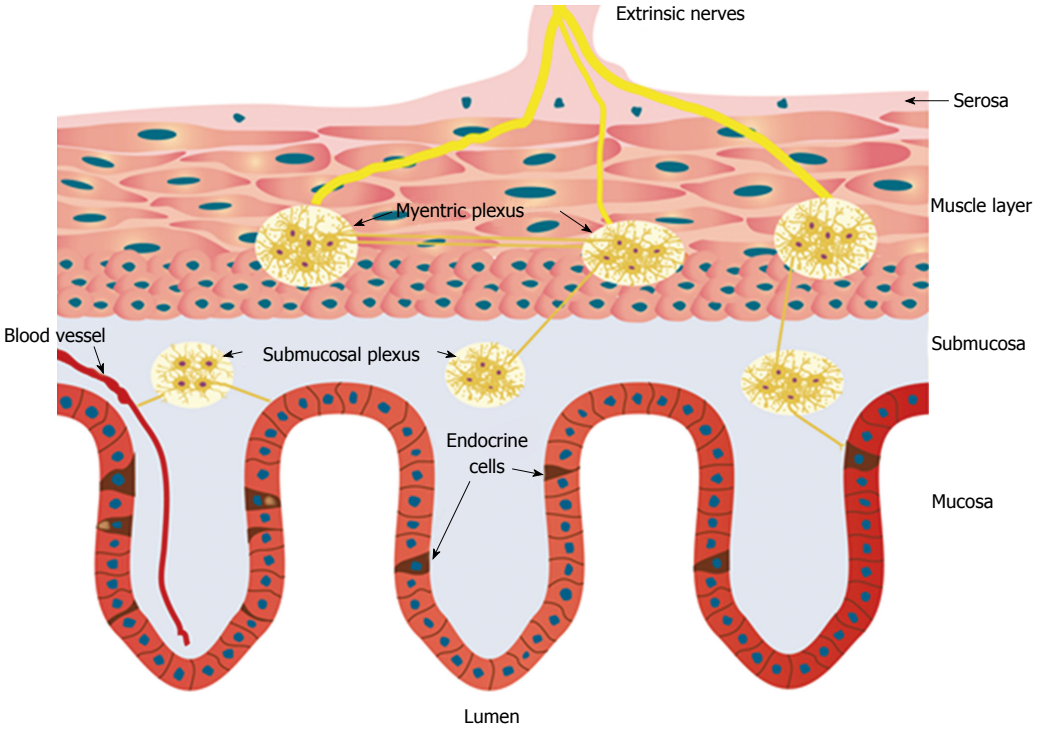

Figure 1 Schematic of the gastrointestinal neuroendocrine regulatory system. The neuroendocrine regulatory system (NES) comprises gastrointestinal (GI) endocrine cells in the mucosa and the enteric nervous system (ENS). The ENS consists of two plexi: one located in the submucosa (the submucosa plexus) and one situated between the longitudinal and circular muscle layers (the myenteric plexus). The GI endocrine cells integrate and interact with each other and with the ENS. The GI NES is an independent system that regulates most of the GI functions and is modulated by the central nervous system.

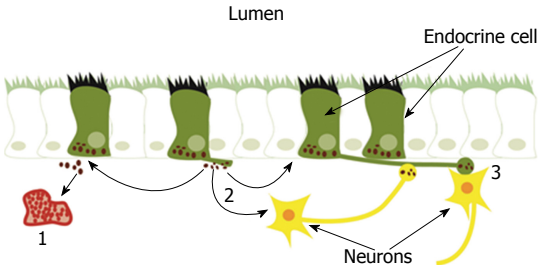

Figure 2 Gastrointestinal endocrine cells have sensory microvilli projecting into the gastrointestinal lumen that register and respond to luminal stimuli by releasing their hormones into the lamina propria. The released hormones exert their effects *via* three modes of action: (1) entering the circulating blood and reaching distant targets (endocrine mode); (2) acting locally on nearby structures (paracrine mode); or (3) *via* synaptic activity. Reproduced from reference 46 with permission from the authors and the publisher.

These data suggest that the GI hormones released in the lamina propria could act locally on close by cells or neurons (paracrine mode), through the circulating blood (endocrine mode), or by afferent and efferent synaptic transmission[94-97] (Figure 2).

Recent observations of GI endocrine cells exhibiting both endocrine and neuron-like characteristics support a long-standing hypothesis about the evolution of the GI NES[98]. The absence of mammalian GI hormonal peptides in the gut of invertebrates, and he occurrence of these peptides in the central nervous system (CNS)[99-101] resulted in the hypothesis that the GI endocrine cells of vertebrates initiated in the nervous system of a common ancestor of invertebrates and vertebrates and then moved during a later stage of evolution into the gut as endocrine cells[98].

The ENS is an independent nervous system within the GI tract that consists of two plexi: one located in the submucosa (the submucosa plexus) and one situated between the longitudinal and circular muscle layers (the myenteric plexus)[102-104]. The neurons of the ENS (about 100 million) are modulated by afferent and efferent nerve fibers from the CNS and the autonomic nervous system[102-104]. The GI endocrine cells integrate and interact with each other and the ENS[105].

The NES regulates GI motility, secretion, absorption, visceral sensitivity, local immune defense, cell proliferation, and appetite[105].

INTERACTION BETWEEN THE GI NES AND INTESTINAL MICROBIOTA

It has long been believed that IBD is caused bacterial infection, and this belief lead to the introduction of salazopyrine (5-aminosalicylic acid-sulfapyridine) for the treat of IBD[106,107]. However, A specific microbe(s) could not be identified as the cause of IBD[106]. Recent studies have shown, however, that intestinal microbiota plays an important role in the pathophysiology of IBD[106]. Thus, low intestinal microbiome diversity and dysbiosis appear to be important factors in the pathophysiology of IBD[106]. The short-chain fatty

acids produced upon fermentation of dietary fibers in the large intestine affect both the immune system and the NES. Butyrate is one of these short-chain fatty acids[108,109]. Butyrate suppresses large intestinal inflammation by inducing T-cell apoptosis, and by suppressing IFN-γ-mediated inflammation[110-112]. The short-chain fatty acids affect several GI peptides, such as PYY and glucagon-like peptide-1[80,113-115]. Furthermore butyrate has been found to affect neurons of the ENS[113,116].

INTERACTIONS BETWEEN THE GI NES AND THE IMMUNE SYSTEM

Several NEPA of the GI NES have been shown to interact with the immune system, including members of the chromogranin/secretogranin family, serotonin, vasoactive intestinal peptide (VIP), members of the neuropeptide Y (NPY) family, substance P, somatostatin, and ghrelin.

Chromogranin/secretogranin family

All of the GI endocrine cell types produce members of the granins family (including chromogranins A and B) that are co-stored and co-released from the GI endocrine cells[34,117-120]. Chromogranin A (CgA) occurs in all GI tract endocrine cell types[121-124]. CgA-derived peptides decrease interleukin (IL)-16 and IL-5 release, and hence decrease the density of lymphocytes at inflammatory sites and thus the proinflammatory action of lymphocytes and monocytes[125-127]. Members of the chromogranin/secretogranin family are believed to exert anti-inflammatory effects.

Serotonin

About 95% of the body serotonin occurs in the GI, of which only 10% occurs in the neurons of the ENS and the rest in the enterochromaffin cells[34,128]. Serotonin is believed to play a pivotal role in intestinal inflammation[34,38,40,125,129,130]. Mast cells, macrophages/monocytes, and T cells are capable of producing serotonin[131]. Serotonin receptors occur in numerous innate IC such as neutrophils, eosinophils, monocytes, macrophages, dendritic cell, mast cells, and natural killer (NK) cells, and in cells of the adaptive immune system such as lymphocytes[130-132]. Serotonin promotes the activation of lymphocytes, whose proliferation protects NK cells and T-helper cells, hinders the apoptosis of IC, and endorses the recruitment of T cells[133-137]. The number of intestinal serotonin cells is decreased in knockout mice lacking T-lymphocyte receptors[125]. Serotonin cells express IL-13 receptors[138]. Against this background, serotonin is considered to be a proinflammatory amine during the inflammatory process.

VIP

VIP is a 28-amino-acid peptide exhibiting structural similarities with secretin[139]. VIP is secreted by neurons, endocrine cells, and IC, and it occurs in almost all body organs[140]. In GI tract, VIP occurs in endocrine cells and neurons of the ENS[141,142]. VIP is believed to be a major immune-regulating neuropeptide that plays an important role in inflammatory disorders, and is considered to be a natural anti-inflammatory agent[142,143].

Both CD4 and CD8T cells produce VIP, especially following antigen stimulation[144,145]. The VIP receptor VPAC1 occurs in lymphocytes, macrophages, monocytes, dendritic cells, microglia, and mast cells[146,147]. VIP inhibits the production of proinflammatory cytokines such as tumor necrosis factor α (TNFα), IL-6, IL-12, iNOS, and promotes the production anti-inflammatory cytokines such as IL-10[148-153]. VIP also inhibits the transcription factors AP-1, nuclear factor-κB (NFκB), CREB, and IRF-1[142,147,153,154], and impairs the acquisition of the macrophage proinflammatory polarization profile[155].

NPY family

The NPY family includes three neuroendocrine peptides that act as hormones and/or neurotransmitters/neuromodulators: NPY, PYY, and pancreatic polypeptide (PP)[156-160]. These peptides consists of 36-amino-acid residues and are structurally related[161]. Whereas NPY is expressed in neurons of the CNS and NES[158,159,162], PYY and PP are expressed by endocrine cells of the ileum, colon, and rectum[163-165]. PP occurs also in endocrine cells in pancreatic islets of Langerhans[160]. NPY and PYY exert similar biological effects[105,161,165], and they act through binding to receptors Y_1 and Y_2[166-169]. T lymphocytes, macrophages, and dendritic cells produce NPY during inflammation[170]. NPY Y_1/Y_2 receptors are localized on IC[171,172], and the binding of NPY to these receptors induces the release of proinflammatory cytokines and nitric oxide from macrophages, neutrophils, and lymphocytes[171,173]. NPY therefore exerts proinflammatory effects in the presence of an inflammatory process. The role of PYY and PP in inflammation is not yet known.

Substance P

Substance P is a member of the tachykinin family and substance P nerve fibers are widely distributed in the GI wall. Substance P is localized in enteric efferent neurons[174-176] and is expressed by several IC including T cells, macrophages, dendritic cells, and eosinophil cells[177-182]. It also plays an important role in the migration of innate IC such as neutrophils and macrophages, and of adaptive IC such as T lymphocytes[183-190]. Furthermore, substance P regulates the proliferation of lymphocytes and modulates the activities of innate and adaptive IC[179,183,191]. Substance P is therefore considered to be one of the main proinflammatory mediators in the GI tract.

Somatostatin

The GI tract and the pancreas contain most of the body

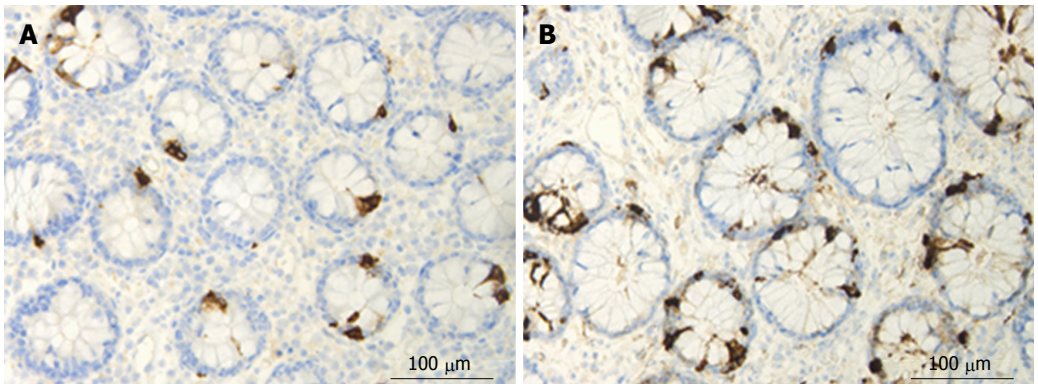

Figure 3 Colonic chromogranin A immunoreactive cells in a control subject (A) and in a patient with lymphocytic colitis (B).

somatostatin[192,193]. About 90% of GI somatostatin is localized in GI endocrine cells, and the remaining 10% is in neurons of the ENS[194]. Somatostatin binds to five membrane G-protein-coupled receptor subtypes (SSTR 1-5)[195]. Several innate and adaptive IC such as monocytes/macrophages, B lymphocytes, T lymphocytes, and dendritic cells expressed these receptors[195-204]. Somatostatin stimulates B-lymphoblast proliferation with the enhancement of immunoglobulin formation[205], inhibits T lymphocytes and granulocyte proliferation, and reduces proinflammatory cytokines such as IFN-g[194,196,206-213]. Somatostatin is considered to be an anti-inflammatory peptide[37,214,215].

Ghrelin

Ghrelin is a peptide composed of 28-amino-acid that occurs mostly in X/A endocrine cells in the oxyntic mucosa of the stomach[42,50,216-221]. Ghrelin performs several functions, including controlling food intake, energy homeostasis, and GI motility[217,218,221-224]. It also mediates the immune response and inflammation[146,225-227]. The anti-inflammatory prosperities of ghrelin are due to it modulating the secretion of pro- and anti-inflammatory cytokines from LPS-stimulated macrophages[225].

NES NEPA IN IBD

NES abnormalities in IBD

Changes in the ENS in IBD such as an increase in the number of enteric neurons, and altered neurotransmitter synthesis and release have been described[228-237]. Similarly, the density of the GI endocrine cells, the proportions of different endocrine cell types, and the release of GI NEPA are affected in both IBD patients and animal models of human IBD.

Chromogranin/secretogranin family: The circulating level of CgA is elevated in IBD patients and is reduced following treatment with certain biological agents[56,238-241]. Patients with IBD exhibit elevated concentrations of fecal CgA and secretogranins[242,243]. The CgA cell density is increased in patients with IBD, and in animal models of human UC and CD, with the exception of trinitrobenzene sulfonic acid (TNBS)-induced colitis[9,117,244-248] (Figure 3). The administration of the proinflammatory cytokines INFγ and TNFα and the induction of colitis by dextran sodium sulfate (DSS) in mice were found to increase the number of CgA cells[249].

Serotonin: The density of colonic serotonin cells is elevated in patients with UC, CD, and lymphocytic colitis[117,250] (Figure 4). The serotonin cell density was also increased in an animal model of human UC (TNBS-induced colitis in rats) and in an animal model of human CD (DSS-induced colitis in rats), as well as in other animal models of human UC and CD, and in IL-2-knockout mice[230,244,245,251,252].

VIP: Studies of VIP in patients with IBD have produced conflicting results. The immunohistochemical examination and quantification of tissue extracts from rectal biopsy samples obtained from patients with UC and CD showed an increased number of VIP-positive nerve fibers and an increased VIP concentration in CD but not in UC[253]. Other studies found that the number of VIP-positive nerve fibers was either decreased or unchanged in patients with UC and CD[245,254,255]. These contradictory results for VIP in patients with IBD could be explained by VIP occurring mostly in neurons of the ENS and that analyzing VIP in small mucosal biopsy specimens obtained during an endoscopic examination does not produce reliable results. However, changes in VIP have been found in animal models of human IBD, especially knockout mice[251]. In *IL-2* gene-knockout mice, the relative volume density of VIP-positive nerve fibers and the level of VIP in tissue extracts were both decreased[251].

NPY family: The density of NPY enteric neurons increased as well as hyperplasia of NPY nerve fibers have been observed in mice with colitis induced either by DSS or streptomycin-pretreated *Salmonella typhimurium*[256,257]. The PYY cell density is increased in patients with UC and lymphocytic colitis as well

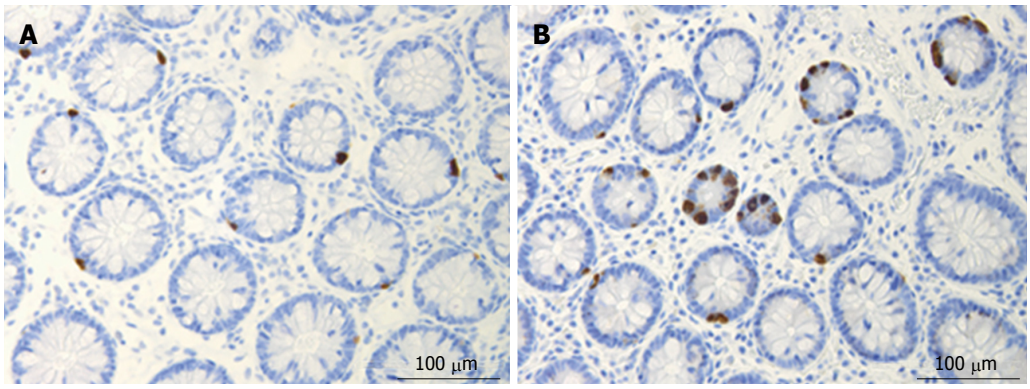

Figure 4 Colonic serotonin cells in a control subject (A) and in a patient with lymphocytic colitis (B).

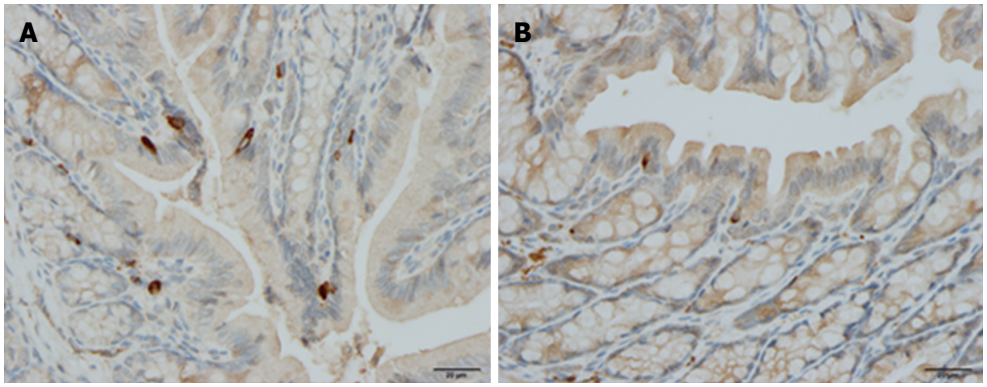

Figure 5 Colonic somatostatin immunoreactive cells in a control rat (A) and in a rat with dextran sulfate sodium-induced colitis (B).

as in colitis induced by DSS in rats and in *IL-2* gene-knockout mice[117,245,250,251]. The PYY cell density is decreased in CD, with this change being correlated positively with the increased disease severity[117]. Similarly, the density of PYY cells was reduced in an animal model of human CD, namely TNBS-induced colitis in rats[244]. The robust positive correlation between the PYY cells and IC found in colitis induced either by DSS, or TNBS in rats is suggestive of an interaction between PYY cells and the IC[244,245]. It is noteworthy that PYY and oxyntomodulin (enteroglucagon) are produced from the same endocrine cell (L cells)[57]. Whereas the density of oxyntomodulin-containing cells is increased in patients with CD and in both DSS- and TNBS-induced colitis, and in IL-2 gene-knockout mice, it is unchanged in patients with UC[118,244,251,258]. The PP cell density is decreased in patients with CD and in colitis induced by either DSS, or TNBS in rats[117,245,248].

Substance P: The levels of substance P are increased in tissue extracts from the colon and in the rectum of patients with UC and CD, and were correlated with disease activity[253,259-261]. The density of nerve fibers immunoreactive to substance P is decreased in the colon of UC patients[262]. The density of substance-P-immunoreactive fibers has been reported to be both increased[253,262] and unchanged[262] in the colon of CD patients. The concentration of substance P in the colon of IL-2-knockout mice is decreased, while substance-P-immunoreactive cells were unchanged[251].

Somatostatin: The number of somatostatin cells is decreased in the colon of patients with IBD, and in animal models of human IBD, except for TNBS-induced colitis where it is increased[245,263-265] (Figure 5).

Ghrelin: The circulating levels of ghrelin are elevated in patients with IBD with active inflammation[266,267]. Moreover, circulating ghrelin levels in UC and CD patients are correlated with TNFα, C-reactive protein, the erythrocyte sedimentation rate, and fibrinogen, and negatively correlated with nutritional status parameters[42,228,268,269].

Possible mechanisms underlying NES abnormalities in IBD

The mechanisms underlying the changes in ENS during inflammation in IBD remain unclear. However, recent studies have shed some light on the possible mechanisms of the inflammation-induced changes in the GI endocrine cells in IBD[258,270].

Whereas changes in GI endocrine cells do occur in UC, CD, lymphocytic colitis, and animal models of human IBD, the nature of these changes differ between the different IBDs and animal models

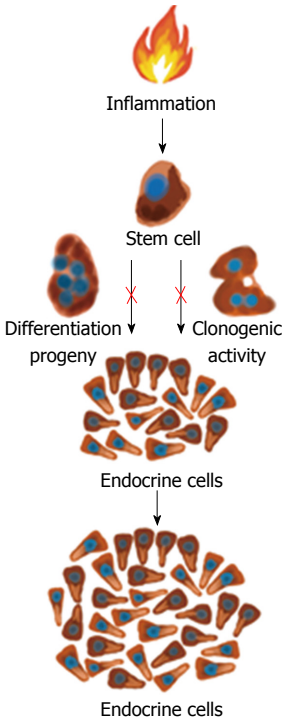

Figure 6 Proinflammatory substances such as cytokines may act on the intestinal stem cells and increase their clonogenic and differentiation progeny so that the density of intestinal endocrine cells increases during active inflammation.

of human IBD[9,117,244-248,250,259]. The changes in GI endocrine cells can be explained by two different mechanisms: abnormal stem cell clonogenic and differentiation progeny toward endocrine cells activities (Figure 6), and switching on and off of the expression of certain GI NEPA (Figure 7).

Abnormal stem cell clonogenic and differentiation activities: Each intestinal crypt contains four to six stem cells that either divide into identical new stem cells (clonogenic) or differentiate into all types of epithelial cells through a series of progenitors[270-281]. This differentiation into epithelial cells includes the secretory and absorptive lineages. The secretory lineage gives rise to endocrine, goblet, and Paneth cells. The absorptive lineage results to absorptive enterocytes[270-281]. In rats with TNBS-induced colitis, which is an animal model of human CD, the colonic density of Musashi-1 (Musi-1) immunoreactive cells was found to be reduced[258]. In contrast, the colonic density of Musi-1 cells was unaffected in rats with DSS-induced colitis, which is an animal model of human UC[268]. Musi-1 is located in both intestinal stem cells and early progenitors[282-284]. These observations indicate that the clonogenic activity of stem cells is affected in an animal model of CD but not in one of UC. This is probably due to the inflammation associated with CD being deep while that associated with UC being superficial.

In rats with both TNBS- and DSS-induced colitis, the colonic Math-1 cell density was found to be unaffected. Math-1 occurs early progenitor in the secretory lineage, and mutant (Math-$1^{-/-}$) mice have no secretory cells[285].

The colonic neurogenin 3 (Neurog3) cell density is reduced in rats with TNBS-induced colitis, while it is increased in rats with DSS-induced colitis[259,270]. Neurog3 is localized in an early progenitor belonging to the secretory lineage, which contributes to the differentiation into endocrine cells[286]. Transgenic mice (Neurog$3^{-/-}$) do not have enteroendocrine cells, but normal densities of goblet and Paneth cells[286-288]. Similar to Neurog3, the colonic NeuroD1 cell density is decreased in rats with TNBS-induced colitis while it is increased in rats with DSS-induced colitis[269,282]. NeuroD1 is located in progenitors originated from Neurog3 progenitors[289,290]. Mice deficient in NeuroD1 lacks certain types of enteroendocrine cells[53,291]. These findings show that the differentiation progeny toward endocrine cells is affected in animal models of human IBD.

Switching the expression of NEPA on and off: As mentioned above, mature GI endocrine cells can express up to seven different hormones[51,52,61-64]. It seems that the changes in the proportion of GI endocrine cells during inflammation occur *via* switching off the synthesis of a neuroendocrine peptide/amine and switching on the synthesis of another[270]. Such a phenomenon has been reported in rats with TNBS-induced colitis (Figure 8).

Hypothesis: It may be speculated that during the inflammation that occurs in active IBD, the IC produce proinflammatory cytokines and other substances that affect the GI stem cells and mature endocrine cells. This will induce abnormal clonogenic and differentiation activities of stem cells. Moreover, the mature endocrine cells switch off the expression of a certain hormone in favor of switching on the synthesis of another hormone. This would result in changes in the total density of endocrine cells and in the proportion of different endocrine cell types. NPA produced by the altered endocrine cells would in return affect the IC *via* their NPA receptors (Figure 9).

CLINICAL IMPLICATIONS

The changes in the intestinal NES associated with inflammation in IBD patients are believed to be useful tools for the diagnosis and follow-up of disease activity. Furthermore, the GI NEA could be candidate targets of IBD treatments. Thus, agonists to anti-inflammatory NEPA and antagonists to proinflammatory NEPA can be used not only for their pharmacological effects but also to correct a pre-existing imbalance in GI NEPA caused by inflammation.

Diagnosis

The colonic CgA cell density has been shown to be a

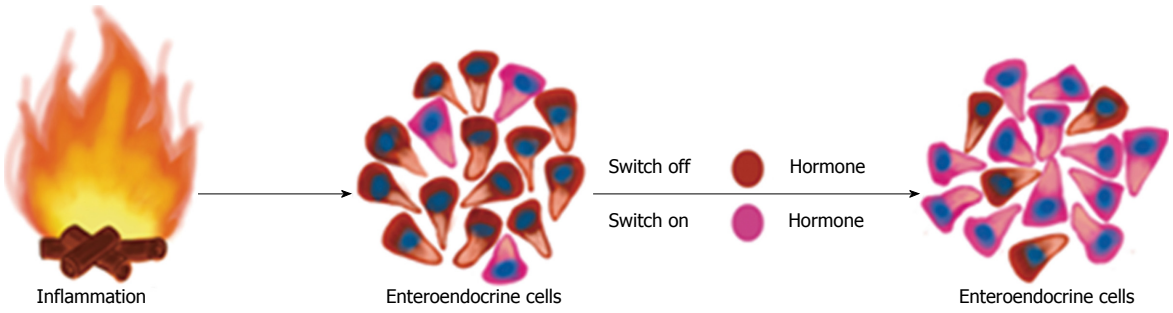

Figure 7 During the inflammatory process, several proinflammatory substances may act on the mature endocrine cells so that they switch off the expression of a certain neuroendocrine peptides/amines and switch on the expression of another neuroendocrine peptides/amines.

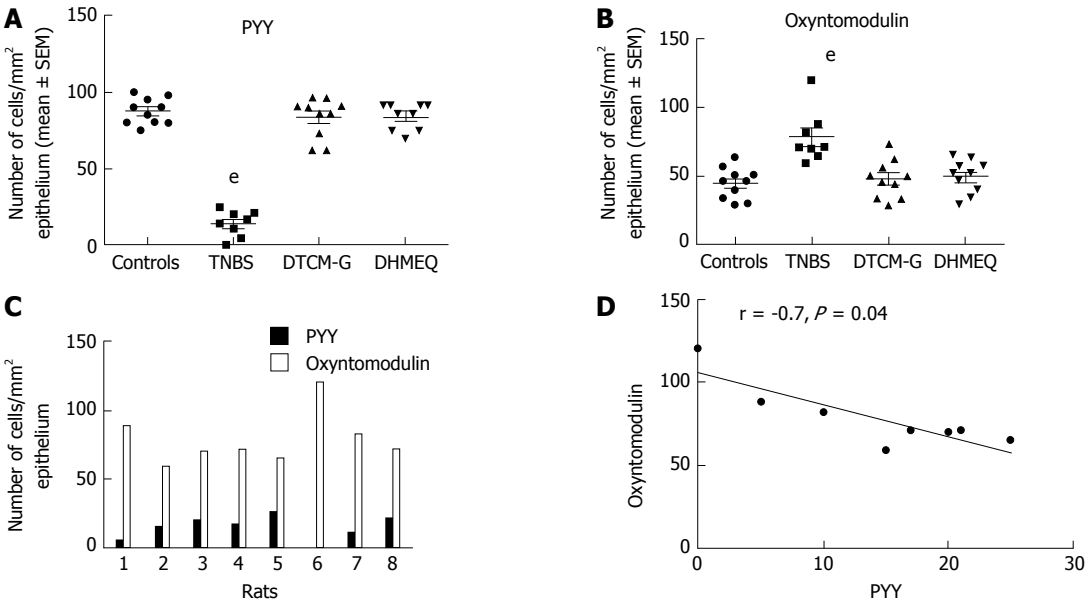

Figure 8 Colonic densities of (A) peptide YY-positive cells and (B) oxyntomodulin (enteroglucagon)-positive cells in control rats, in rats with trinitrobenzene sulfonic acid (TNBS)-induced colitis, and in rats with TNBS-induced colitis treated with 3-[(dodecylthiocarbonyl)-methyl]-glutarimide (DTCM-G, an activator protein-1 inhibitor) and dehydroxymethylepoxyquinomicin (DHMEQ, a nuclear factor-κB inhibitor). Densities of PYY-positive and oxyntomodulin-positive cells in each rat of the TNBS group (C), and their correlation (D). $^{e}P < 0.001$ *vs* controls. Reproduced from reference 274 with permission from the authors and the publisher. PYY: Peptide YY.

good biomarker for diagnosing lymphocytic colitis, with a high sensitivity and specificity[9]. The blood and fecal levels of CgA and secretogranins have been proposed for the diagnosis and follow-up of the disease activity in IBD[56,238-243].

Treatment

Treatment with CgA-derived peptides of mice with DSS-induced colitis decreases the disease activity index, macroscopic and histology scores, and the colonic levels of IL-1β, IL-6, and TNFα[34].

Antagonists of serotonin receptors 5-HTR3 and 5-HTR7 such as tropisetron, granisetron, ondansetron, ramosetron, and SB-269970 have shown anti inflammatory effects in animal models of human IBD[292-300]. These serotonin receptor antagonists act *via* reducing the ynthesis of proinflammatory cytokines IL-1, IL-6, and TNFα. The usefulness of selective inhibition of mucosal serotonin by these receptor antagonists in the clinical treatment of IBD remains to be determined[301].

VIP is believed to be a potential agent for treating IBD since it targets both the innate and adaptive immune responses and inhibits the secretion of numerous proinflammatory cytokines *via* its actions on AP-1 and NFκB[142]. Administering VIP reduced inflammation in TNBS-induced colitis in mice[142], and it has been used successfully in the clinic as an inhalator for treating pulmonary hypertension and sarcoidosis[142]. However, delivering VIP is problematic since it is degraded rapidly in the blood circulation (with a half-life of only 1-2 min) and systemic administration causes both cardiovascular and intestinal side effects[140,302,303].

NPY occupies a key position during the inflammatory process in IBD, and NPY antagonists could be potentially useful in treatments for the inflammation in IBD[43]. This suggestion is supported by observations made in animal models of UC, namely DSS-induced colitis in rats[303,304]. Treatment with NPY

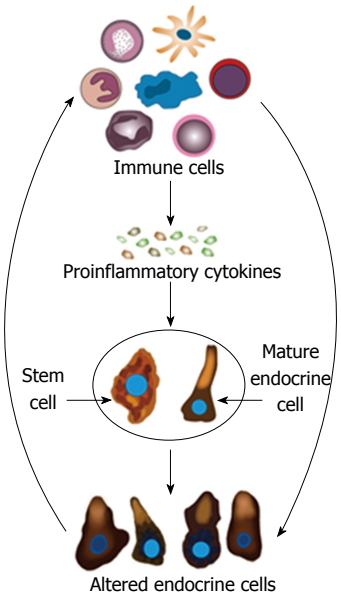

Figure 9 Schematic of the possible mechanisms underlying the changes in gastrointestinal endocrine cells in inflammatory bowel disease. In active inflammatory bowel disease, the immune cells (IC) produce proinflammatory cytokines and other substances that affect the gastrointestinal (GI) stem cells and mature endocrine cells. Thus, abnormal clonogenic and differentiation activities are induced in stem cells. Moreover, the mature endocrine cells switch off the expression of certain hormones in favor of switching on the synthesis of other hormones. This would change the GI endocrine cell density and alter the proportions of the various endocrine cell types. The NPA released by the altered endocrine cells would in return affect the IC *via* their NPA receptors.

antisense oligodeoxy-nucleotides in colitis induced by DSS in rats reduced the inflammation as well the concentration of NPY, TNFα, p-Akt, and asp-NFκB[304]. The NPY Y_1 receptor is involved in several biological functions[302-305], and so using an NPY Y_2 receptor antagonist is preferable in future clinical implications in order to minimize side effects.

Blocking substance P receptors with either substance P antibodies or with CP 96345 (NK-1R antagonist) diminished jejunal inflammation[306,307].

The effects of ghrelin treatment were tested in an animal model of human UC, namely TNBS-induced colitis in mice[147,307]. Ghrelin decreased both the clinical and histopathological severity of the colitis and increased the survival rate[147,307]. These effects seem to be attributable to the decrease of both inflammatory and Th1-driven autoimmune responses *via* affecting several inflammatory mediators, and by the involvement of IL-10/transforming growth factor-ß1-secreting regulatory T cells[147,307].

CONCLUSION

IBD is a chronic disease with unknown etiology that affects a large number of individuals worldwide. About 80% of the body IC are in the GI tract close to the NES of the gut. Several innate and adaptive IC express and release a considerable number of GI NEPA. Furthermore, the IC possess receptors for several GI NEPA. The enteroendocrine cells and the neurons of the ENS are abnormal during the inflammation that occurs in IBD. The changes in these two compartments of the GI NES are strongly correlated with the changes in IC in active IBD. These observations indicate the presence of interactions between GI NEPA and the immune system in active IBD. These interactions seem to play a significant role in the pathophysiology of IBD. The changes in the GI NEPA during active IBD occur in proinflammatory GI NEPA such as serotonin, members of the NPY family, and substance P, and in anti-inflammatory GI NEPA such as members of the chromogranin/secretogranin family, VIP, somatostatin, and ghrelin. Antagonists to the proinflammatory GI NEPA and agonists to the anti-inflammatory GI NEPA could therefore be useful tools for treating IBD.

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